REMARKS

A. The Status of the Claims and the Amendments

Claims 1, 47, 49-51, and 55 are pending. Claims 2-46, 48, 52-54, and 56-59 were previously canceled. By the present amendment, claims 1 and 49 have been amended to more particularly define the Applicant's invention and to claim it with greater specificity. As amended, the amendments to claims 1 and 49 are supported by the specification and the original claims. No new matter have been added. It is submitted that the amendments place the claims in condition for allowance or a better condition for appeal. Entry of the amendments is respectfully requested.

B. Rejection Under 35 U.S.C. § 103(a)

Claims 1, 47, 49-51, and 55 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Patent No. 5,498,421 to Grinstaff et al. in view of U.S. Patent No. 6,193,951 to Ottoboni et al., U.S. Patent No. 5,469,854 to Unger et al., and U.S. Patent No. 4,960,595 to Hirota et al. (page 2, lines 10-12 of the Office Action). This rejection is respectfully traversed on the following grounds.

The legal standard that has to be satisfied to establish a *prima facie* case of obviousness was discussed previously. It is submitted that this standard has not been met. More specifically, Grinstaff et al. fail to describe shells made of "a drug-free outer lipid layer and a gas-free inner oil layer" as recited in claim 1, as amended. Indeed, Grinstaff et al. neither disclose nor suggest any liposomal structures having a separate inner oil layer disposed over the lipid layer. Nor do Grinstaff et al. disclose or suggest a gas-filled void surrounded by the gas-free oil layer. Likewise, there is nothing in Grinstaff et all. teaching or suggesting an embodiment having a drug dispersed in the oil layer, while the lipid layer remains free of drugs, as required by claim 1.

To the contrary, Grinstaff et al. teach that the oil and the gas are mixed (FIG. 1 and col. 7, lines 34-35). All that is taught by Grinstaff et al. is the use of protein (e.g., albumin) shells encapsulating a biologic agent (col. 9, lines 1-4), and that a gas and an oil can be fluorinated (FIG. 1 and col. 7, lines 34-35). Accordingly, Grinstaff et al. fail to disclose or fairly suggest every element of claim 1, as amended.

To cure the above-described deficiencies of Grinstaff et al., the Examiner has proposed to combine the teachings or alleged suggestions of Grinstaff et al. with those of Ottoboni et al., Unger et al., and Hirota et al. The Applicant respectfully submits that neither the references cited by the Examiner nor the general state of the art would motivate one having ordinary skill in the art to make such a combination.

It is submitted that it is unclear from the face of Grinstaff et al., Ottoboni et al., Unger et al., and Hirota et al., why these references should be combined. The only reason given by the Examiner is that "polymeric shells and their phospholipid modified analogs are art recognized functional equivalents" and "the use of phosphatidic acid is conventionally practiced to improve stability" (see, page 3, lines 18-21 of the Office Action). The Examiner has not provided any other explanation or justification. It is respectfully submitted that just a possibility of the existence of an embodiment comprising features disclosed in several references is not in itself sufficient to provide motivation for making such a combination. More is required, e.g., showing that combining the references is desirable.

The law requiring a suggestion or motivation in order to be able to combine references is. well established. When, as in this case, the motivation to combine the teachings of the references is not immediately apparent, it is the duty of the examiner to explain why the combination of the teachings is proper. Ex parte Skinner, 2 USPQ2d 1788 (Bd. Pat. App. & Inter. 1986). The Applicants respectfully submit that the Examiner has not fulfilled this duty.

It is also well established that in making rejections over the prior art, the Patent Office "may not, because it may doubt that the invention is patentable, resort to speculation, unfounded assumptions or hindsight reconstruction to supply deficiencies in its factual basis." In re Warner, 379 F.2d 1011, 1017, 154 USPQ 173, 178 (CCPA 1967), cert. denied, 389 U.S. 1057, 19 L. Ed. 2d 857, 88 S. Ct. 811 (1968). It is submitted that the fact that the Examiner's has not provided a reasoned factual statement explaining the desirability of combining the teachings of the references amounts to making such "unfounded assumptions or hindsight reconstruction."

For example, with respect to Ottoboni et al., the Examiner has asserted that the inner layer of the microspheres "can further provide drug delivery properties (see, page 2, line 16 of the Office Action). The Applicants respectfully point out that claim 1 of the present application requires both to have the drug dispersed in the inner oil layer and the presence of "a drug-free outer lipid layer." While Ottoboni et al. may mention the presence of the drug in the inner layer, it definitely does not teach or suggest the drug-free outer lipid layer. Indeed, Ottoboni et al. explicitly provide that the inner layer is to be used for drug delivery if the outer layer alone does not have enough capacity. One skilled in the art fairly reading this teaching (i.e., col. 4, lines 1-3) would undoubtedly understand it as a direction to utilize the outer layer for drug delivery first, and only use the inner layer as an additional reservoir for the drug, i.e., when the capacity of the outer layer is insufficient for some reason.

Thus, there is clearly no motivation to combine the Grinstaff et al., Ottoboni et al., Unger et al., and Hirota et al. since, in order to meet all the limitations of claim 1, such a combination must lead to an embodiment that includes a drug-free outer lipid layer, which is not what Ottobani et al. recommend.

Accordingly, the Applicants respectfully submit that the teachings of Grinstaff et al., Ottoboni et al., Unger et al., and Hirota et al. are not properly combinable due to lack of motivation to do so. However, even if, *arguendo*, there were the motivation to

combine Grinstaff et al., Ottoboni et al., Unger et al., and Hirota et al., the combination of the teachings of the four references would still fail to describe or to suggest every limitation of claim 59, as amended.

Indeed, Ottoboni et al. describe the microspheres having an inner and an outer layer (col. 2, lines 56-60). The microspheres can include paraffin (Example 3, col. 8, line 10), which as correctly pointed out by the Examiner may fall within the limitation of oil recited in claim 1 (page 2, lines 17-18 of the Office Action). However, Ottoboni et al. neither teach nor suggest that paraffin form the inner layer of the shell. Nor, as discussed above, is there any teaching or suggestion in Ottoboni et al. that a drug can be dispersed in paraffin (i.e., the inner layer) **unless the drug is also present** in the outer layer. As discussed above the drug cannot be present in the outer layer as this will contradict the limitations of claim 1.

With regard to Unger et al., this reference teaches gas-filed liposomes (abstract; col. 4, lines 44-45) having a lipid shell (col. 11, lines 40-50) and biologically active materials optionally incorporated into the lipid layer (col. 13, lines 18-24). Unger et al. fail to teach or suggest a separate oil inner layer disposed over the lipid outer layer, or a gas-filled hollow core surrounded by the gas-free oil layer. Thus, even if the teachings of Grinstaff et al. and Unger et al. were to be combined, the combination still fails to disclose or suggest every limitation of claim 1, as amended.

Hirota et al. do not help to cure the above-discussed deficiencies, because there is nothing in Hirota et al. describing or suggesting a double-layer shell comprising separate lipid and oil layers, encapsulating a gas, and having a drug dispersed in the oil layer but not in the lipid layer, as required by claim 1.

Accordingly, even if the teachings of Grinstaff et al., Ottoboni et al., Unger et al., and Hirota et al., were to be combined, any combination of all four references neither explicitly teaches nor implicitly suggests every limitation of claim 1.

In view of the foregoing, claim 1 is patentably distinguishable over Grinstaff et al., Ottoboni et al., Unger et al., and Hirota et al., or over any combination thereof. Each of claims 47, 49-51 and 55 depends on claim 1, directly or indirectly, and is considered patentable for at least the same reason. Withdrawal of the rejection and reconsideration are respectfully requested.

CONCLUSION

In view of the above amendments and remarks, reconsideration and favorable action on all claims are respectfully requested. In the event any matters remain to be resolved, the Examiner is requested to contact the undersigned at the telephone number given below so that a prompt disposition of this application can be achieved.

No fee is deemed necessary in connection with the filing of this response. However, if any fee is required, authorization is hereby given to charge the amount of any such fee, or credit any overpayment, to Deposit Account No. 07-1896 referencing the above-identified attorney docket number. A copy of the Transmittal Sheet is enclosed.

Respectfully submitted,

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Victor Repkin
Attorney for Applicants
Registration No. 45,039
Telephone: (858) 638-6664
Facsimile: (858) 677-1465

DLA PIPER RUDNICK GRAY CARY US LLP
4365 Executive Drive, Suite 1100
San Diego, California 92121-2133
USPTO Customer Number 28213